REMARKS

Claim 2 is amended to add "wherein the concentration of the inhibitor in the aqueous nutrient medium is within a range that gives less than a 50 % reduction of cell growth as compared to cell growth in the absence of the inhibitor under carotenoids-producing conditions and cell growth is determined by measuring the optical density of a sample of the cultured medium at 660 nm." Support for this amendment is found in the Specification at, for example, Paragraph 18, Paragraph 25 including Table 1, Paragraph 29, Table 2, and Paragraphs 15-17; and original claims 18, 20 and 21. *In re Gardner*, 177 USPQ 396, 397 (CCPA 1973), and MPEP §§ 608.01(o) and (l).

Claim 2 is also amended to delete "including" and replace it with "which include." Support is found in the Specification at, for example, Paragraphs 4, 5, 15, 20, and Example 2 (Paragraphs 27-30).

Claim 2 is also amended to delete "broth" and replace it with "medium." Support for this amendment is found in the Specification at, for example, Paragraph 20, lines 1-4.

Claim 3 has been amended to recite "*Xanthophyllomyces dendrorhous* (*Phaffia rhodozyma*) ATCC96594, redeposited under accession No. ATCC 74438." The redeposit information (accession No. ATCC 74438) which has been added by the amendment refers to the redeposit of the original *Phaffia rhodozyma* ATCC96594 deposit disclosed in Paragraph 24, line 1, and Paragraph 27, line 1; and in original claim 3.

Claim 19 is amended to revise the dependency.

Claim 18 is cancelled without prejudice.

Claim 22 is added which depends from claim 3. Support for this claim is found in the Specification at, for example, Paragraph 14; and Examples 1 and 2 (Paragraphs 24-30); and original claim 17.

Claim 23 which is dependent on claim 2 is added. Support for this claim is found in the Specification at, for example, Example 1 (Paragraphs 24-26, including Table 1).

Claim 24 which is dependent on claim 2 is added. Support for this claim is found in the Specification at, for example, Example 2 (Paragraphs 27-30, including Table 2).

No new matter has been added by any of the claim amendments.

Indefiniteness Rejection

Claims 2-3, 13, and 15-21 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. (Paper No. 20080711 at 2.)

In making the rejection, the Examiner asserted that "[c]laim 2 is confusing in the use of the phrase 'a substrate for producing carotenoids including astaxanthin'." (Id.) The Examiner also asserted that "[c]laim 2 is vague, indefinite and confusing in the recitation of 'greater than'." (Id.)

The Examiner also asserted that "[c]laim 18 is confusing in that applicant fails to set forth the criteria that define a 'concentration of the said inhibitor' other than providing a functional definition of 'inhibitor' as 'giving less than ... reduction of the cell growth' of undefined microorganisms using undefined inhibitors." (Id. at 2-3). The

Examiner also asserted that "it is unclear how the concentration [of inhibitor] correlates with the production of 'greater' astaxanthin content...". (Id. at 3.)

In the "Response to Arguments" section of the Action, the Examiner asserted that "not all of the members of genus *Xanthophyllomyces (Phaffia)* have the same requirements and react the same way to inhibitors. Therefore, the amount required to meet the claim limitations is at least ambiguous and variable depending on the strain cultured and on the culturing conditions therefor." (Id.)

The Examiner alleged that the claims are overly broad, and asserted that the example "pertains specifically to the combination of culturing *Phaffia rhodozyma* ATCC 96594 using the [elected species of] inhibitor ... in various specific concentrations." (Id. at 4.)

As noted above, claim 2 has been amended to recite "carotenoids which include", to provide further clarity.

To further prosecution in the present application, claim 2 has also been amended to recite, "wherein the concentration of the inhibitor in the aqueous nutrient medium is within a range that gives less than a 50 % reduction of cell growth as compared to cell growth in the absence of the inhibitor under carotenoids-producing conditions and cell growth is determined by measuring the optical density of a sample of the cultured medium at 660 nm."

The Examiner appeared to express concern over the fact that various process parameters such as inhibitor concentration as well as "the strain cultured and ... the culturing conditions therefore", are not recited in the claims. (Paper No. 20080711 at 3). The legal standard for definiteness, however, is whether a claim

reasonably apprises those of skill in the art of its scope. *In re Warmerdam*, 31 USPQ 2d 1754, 1759 (Fed. Cir. 1994). Here, the amended claims meet that standard by explicitly reciting "wherein the concentration of the inhibitor in the aqueous nutrient medium is within a range that gives less than a 50 % reduction of cell growth as compared to cell growth in the absence of the inhibitor under carotenoids-producing conditions and cell growth is determined by measuring the optical density of a sample of the cultured medium at 660 nm."

We also note that the Specification discloses a simple way to identify an inhibitor concentration which gives less than a 50% reduction of cell growth as compared to cell growth in the absence of the inhibitor under carotenoids-producing conditions, as claimed. As disclosed in Examples 1 and 2, cell growth may be determined by measuring the optical density (OD) at 660 nm. In particular, Example 1 concerns the "Effect of Addition of the Squalene Synthase Inhibitor on the Cell Growth of *Phaffia rhodozyma*". As disclosed in Paragraph 26, "About 23% inhibition of the cell growth was observed at day 2 by 5.0 μg/ml of the inhibitor." Percent reduction of cell growth can be determined in the manner in which the noted 23% reduction was determined.

Ample guidance is provided in the Specification for one of skill in the art to determine the percent reduction of cell growth using the disclosed method. As disclosed in Paragraph 25, "An aliquot of the culture was withdrawn occasionally during the cultivation, and optical density at 660 nm was measured ... for analysis of the cell growth." The results are disclosed in Table 1 within Paragraph 25. In order to calculate the 23% reduction indicated, one would note that the disclosed OD (at 660 nm) at day 2

in the presence of 5.0 μg/ml inhibitor is 12.3. Relative to the cell growth on day 2 in the absence of inhibitor, i.e., 0 μg/ml, in which the OD (at 660 nm) is 15.9, this is about a 23% reduction or inhibition of cell growth. The 5.0 μg/ml concentration of the inhibitor that afforded the about 23 % reduction in cell growth is thus identified as a concentration of the inhibitor that is within the range that gives less than a 50 % reduction of cell growth as compared to cell growth in the absence of the inhibitor. Accordingly, one skilled in the art would readily be able to identify whether or not a given concentration of a given inhibitor is within the range that gives less than a 50 % reduction of cell growth as compared to cell growth in the absence of the inhibitor.

In addition, we draw the Examiner's attention to the An article which the Examiner has cited in the § 103 rejection. On page 118, left-hand column, second paragraph, An disclose the incorporation of several inhibitors of sterol biosynthesis or carotenoid synthesis in YM agar given to *P. rhodozyma* strains in order to identify strains resistant to sterol biosynthesis inhibitors. An disclose that "[c]oncentrations [of sterol biosysnthesis inhibitor] that gave ≥ 90% kill were determined". (Lines 6-7.) Thus, An has defined certain concentrations of sterol biosynthesis inhibitors by way of an identified result occurring from such concentration. This evidences that reciting inhibitor concentrations in terms of those which give a certain result, *e.g.*, percentage of kill or a certain percentage of reduction in cell growth, as claimed, would be well understood by one of ordinary skill in the art.

Furthermore, the Examiner has not only cited the An document in the § 103 rejection, but has pointed specifically to Page 118, paragraph 2, which contains the above-cited disclosure regarding "[c]oncentrations that gave ≥ 90% kill". (Paper No.

20080711 at 6.) Tellingly, the Examiner had no problem ascertaining the meaning of the functional language in An.

The Specification has thus provided sufficient guidance regarding the concentration of inhibitor even if, as the Examiner asserted, there is "[variability] depending on the strain cultured and on the culturing conditions therefore." (Id. at 3.) Moreover, the claims apprise one skilled in this art of the scope of the invention, and 35 USC § 112, second paragraph, does not require more.

In addition, the Specification provides ample guidance regarding the claim term "greater than", as recited in the clause "wherein the astaxanthin content of the isolated carotenoids is ***greater than*** that which results from cultivating in the absence of an inhibitor of biosynthesis of sterols from farnesyl pyrophosphate." For example, we refer the Examiner to Example 2 of the Specification at Paragraphs 27-30. Paragraphs 28 and 29 disclose a method for "analysis of the content of astaxanthin". HPLC was performed on samples in the presence of inhibitor and without inhibitor. Table 2 discloses relative values of astaxanthin content. For nearly all concentrations of inhibitor and test conditions, the relative value of astaxanthin content is greater than, i.e., higher than the value for the sample without inhibitor. Moreover, Paragraph 30 discloses that "[a]staxanthin production [in the presence of inhibitor] was enhanced in all conditions tested."

In addition, the Examiner has not made any factual determination that establishes that one of ordinary skill in the art would not have been able to ascertain with a reasonable degree of precision and particularity the area set out and circumscribed by the claims based upon the term "greater than", as used in claim 2.

Relative terms are not *per se* indefinite. And merely characterizing "greater than" as a "word of degree" does not satisfy the Examiner's burden.

Furthermore, the law is clear that the breadth of a claim is not to be equated with indefiniteness. *SmithKline Beecham Corp. v. Apotex Corp.*, 74 USPQ2d 1396 (Fed. Cir. 2005), citing *In re Gardner*, 166 USPQ 138 (CCPA 1970). In *In re Gardner*, the Court of Customs and Patent Appeals considered whether claims drawn to a method of producing antidepressant activity, which comprises internally administering certain compounds, satisfied the requirements of 35 USC § 112, second paragraph. 166 USPQ 138. The Court stated that the claims "are merely broad [in not naming a host] and cover the ... method when administered or applied to *any* host capable of enjoying the benefits of an antidepressant drug." (Id. at 140) (emphasis in original). Moreover, the recitation of administering "an effective amount" was also determined to be sufficient. (Id.) The present claims similarly meet the requirements of 35 USC § 112. Amended claim 2 recites "a microorganism which is capable of producing carotenoids which include astaxanthin and belonging to the genus *Xanthophyllomyces (Phaffia)* in the presence of an inhibitor of biosynthesis of sterols from farnesyl pyrophosphate". The Examiner has not indicated why one skilled in the art would allegedly not be able to ascertain what is defined by the "microorganism" or the "inhibitor" as recited in claim 2.

"In rejecting a claim under the second paragraph of § 112, ***it is incumbent on the Examiner to establish that one having ordinary skill in the art would not have been able to*** ascertain the scope of protection defined by the claim when read in light of the supporting specification." *Ex parte Cordova*, 10 USPQ2d 1949,

1952 (Board of Pat. App. and Int. 1989), citing *In re Moore*, 169 USPQ 236 (CCPA 1971). This, the Examiner has not done.

For each of the foregoing reasons, it is submitted that the rejection cannot stand and should be withdrawn.

It is respectfully submitted that the rejection has been rendered moot. Reconsideration and withdrawal of the rejection are requested.

Enablement Rejection

Claim 3 was rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. (Paper No. 20080711 at 4.)

In making the rejection, the Examiner asserted that "Applicant indicates that the strain of claim 3 was redeposited at the ATCC on April 8, 1998. However, the claim pertains to ATCC96594, the old number. The new deposit accession number is not mentioned with any specificity in the Response. Thus it is unclear which deposit is addressed by applicant's averments at page 11, paragraph 1 of the Response. Moreover, the correct deposit number should be in the claim." (Id. at 5-6.)

In addition, the Examiner asserted that "the deposit must be referred to in the body of the specification...". (Id. at 5.)

To address the Examiner's concerns, Claim 3 has been amended to recite "*Xanthophyllomyces dendrorhous* (*Phaffia rhodozyma*) ATCC96594, redeposited under accession No. ATCC 74438." In addition, the Specification has also been amended in Paragraphs 24 and 27 to provide the redeposit accession number.

Although we disagree with the Examiner's position, with a view toward furthering prosecution, the following is provided upon information and belief: a strain of *Xanthophyllomyces (Phaffia)* according to the present invention was originally deposited with the American Type Culture Collection (ATCC) (located at 10801 University Blvd., Manassas, VA 20110-2209). The strain was assigned accession no. ATCC96594. Subsequently, the strain was redeposited with the ATCC under accession No. ATCC 74438 on April 8, 1988 pursuant to the Budapest treaty. All restrictions on the availability to the public of the material so deposited will be irrevocably removed upon the granting of a patent.

In view of the foregoing, it is respectfully submitted that the rejection has been rendered moot. Withdrawal of the rejection is requested.

Obviousness Rejection

Claims 2-3, 13, and 15-21 were rejected under 35 U.S.C. § 103(a) as being unpatentable over An *et al.*, Applied and Environmental Microbiology, Jan. 1989, Vol. 51, p. 116-124 ("An") "taken with" Brown *et al.*, Phenoxypropylamines: A New Series of Squalene Synthase Inhibitors, J. Med. Chem., 1995, Vol. 38, no. 21, p. 4157-4160 ("Brown"). (Id. at 6.) In making the rejection, the Examiner asserted that "the reasons [for the rejection are] as stated in the last Office action and the further reasons [provided]." (Id.)

The An document was summarized in the Response to Office Action Including Amendment that was filed May 29, 2008 ("the prior Response") on pages 12-13.

Brown was summarized in the prior Response at page 16.

In making the rejection, the Examiner asserted that "An *et al.* discloses a method of culturing strains of *Xanthophyllomyces (Phaffia)* that is capable of producing carotenoids in the presence of an inhibitor of squalene synthase. See, e.g., page 118, paragraph 2. Although the reference reports that the method of culturing in the presence of an inhibitor of sterol synthesis did not appear to have greater astaxanthin content, this was not, in fact, measured with any precision, but rather only eye-balled. Therefore one of ordinary skill in the art would reasonably have expected some increase even though it might not be readily apparent to the naked eye." (Paper No. 20080701 at 6.)

The Examiner acknowledged that in An "the inhibitor of squalene synthase is not a phenoxypropylamine compound and is not specifically [3-(3-allyl-biphenyl-4-yloxy)propyl]-isopropyl-amine.

In attempting to fill the gap, the Examiner asserted that "Brown et al. adequately demonstrate that this phenoxypropylamine compound is known in the art as a squalene synthase inhibitor." (Id. at 7.)

The Examiner concluded that "it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to modify the process of An et al. by culturing *Xanthophyllomyces (Phaffia)* for the production of a variety of carotenoids including astaxanthin using a different inhibitor of squalene synthase inhibitor such as the phenoxypropylamine compound [3-(3-allyl-biphenyl-4-yloxy)-propyl]-isopropyl-amine for the expected benefit of maximizing the yield of the valuable

compounds carotenoids including astaxanthin useful as food additives and in pharmaceutical applications." (Id.)

In the "Response to Arguments" section of the Action, the Examiner asserted, *inter alia*, "It is noted ... that the reference pertains to 'resistance' to sterol inhibitors after mutation events for selection purposes wherein certain concentrations are used... In addition, the extent of 'greater' astaxanthin content in the present claims is not defined with any particularity. Therefore, the amount of the increase intended cannot be determined with any precision and encompasses even a tiny increase which may not be readily detectable with the naked eye." (Id. at 8.)

The Examiner also asserted that An "pertains to selection of mutants that produce carotenoids and which demonstrate 'resistance' to inhibitors, while the invention as claimed is directed to the 'presence' of an inhibitor or to the 'presence' a [sic] specific inhibitor." (Id.) The Examiner further asserted that "the reference clearly suggests that sterol biosynthesis inhibitors are expected to be involved in increases of carotenoid production including astaxanthin." (Id.)

The Examiner further asserted:

> In addition, the results of Table 2 of the as-filed specification show that at day 4 of cultivation the results are better without addition of the specific squalene synthase inhibitor [3-(3-allyl-biphenyl-4-yloxy)-propyl]-isopropyl-amine than with the addition of 5 µg/ml even for the specific strain ATCC 96584 in a specific medium. Thus, it is apparent that the length of cultivation as well as the concentration of the specific inhibitor [3-(3-allyl-biphenyl-4-yloxy)propyl]-isopropyl-amine affect the astaxanthin content obtained for a specific high producing strain such as *Xanthophyllomyces (Phaffia)* ATCC 96584. Yet only in dependent claim 3 is this specific strain of *Xanthophyllomyces (Phaffia)* cultured. Thus, the results presented in the specification cannot be readily extrapolated to the broad invention as claimed, since the results obtained suggest to one of ordinary skill in the art that the

> effects on carotenoid and astaxanthin production are dependent on the strain of *Xanthophyllomyces (Phaffia)* cultured as well as the type and concentration of inhibitor used in the culturing process." (Id. at 8-9.)

The Examiner concluded that "[t]he claims are not commensurate in scope with the arguments or the results in the specification." (Id. at 9.)

Arguments regarding An which were presented in the Response to Office Action Including Amendment filed May 29, 2008 ("the prior Response"), in response to both the § 102 rejection (now withdrawn) and the § 103 rejection (now maintained), are incorporated here.

To further prosecution in the present application, claim 2 has been amended to add, *inter alia*, "wherein the concentration of the inhibitor in the aqueous nutrient medium is within a range that gives less than a 50 % reduction of cell growth as compared to cell growth in the absence of the inhibitor under carotenoids-producing conditions and cell growth is determined by measuring the optical density of a sample of the cultured medium at 660 nm."

Respectfully, we submit that the Examiner has erred in mischaracterizing An. An's disclosure relating to use of a sterol biosynthesis inhibitor differs entirely from the claimed process. An discloses ways of "[trying] to develop selection procedures for astaxanthin overproduction." (Page 118, right col., 17th and 16th lines from the bottom.) Regarding one of these procedures, An discloses that "[s]everal inhibitors of sterol biosynthesis ... or carotenoid biosynthesis were incorporated in YM agar, and ***resistant colonies were evaluated for astaxanthin production***." (Page 118, left col., lines 6-8) (emphasis added.) In indicating how resistant strains were identified, An discloses that "***[c]oncentrations [of inhibitor] that gave [greater than or equal to] 90% kill were***

determined, and then 30 to 100 YM agar plates containing the inhibitors were inoculated with sufficient cells to give 100 to 500 surviving colonies." (Page 118, left col., lines 11-14) (emphasis added.)

An's use of an inhibitor concentration that gave [greater than or equal to] 90% kill fails to teach or suggest "cultivating a microorganism" using the presently claimed concentration of inhibitor which is recited as "within the range that give less than a 50% reduction of cell growth as compared to cell growth in the absence of the inhibitor under carotenoids-producing conditions". An sets out to find resistant colonies, and in the process, uses a concentration that kills greater than or equal to 90% of the microorganisms. For a given inhibitor of biosynthesis of sterols from farnesyl pyrophosphate, therefore, ***An discloses using significantly higher inhibitor concentrations than those used in the claimed process***. Moreover, since An identifies strains resistant to inhibitors of biosynthesis of sterols from farnesyl pyrophosphate, An has no concern in comparing cell growth of the surviving, resistant strains to cell growth in the absence of the inhibitor. An bypasses the mechanism of inhibition of biosynthesis of sterols from farnesyl pyrophosphate by using resistant strains. An's disclosed procedure which seeks to employ a mechanism in which a microorganism is rendered resistant to the inhibitor, while killing most strains in the process, could hardly be further from the claimed process of "cultivating ... in the presence of an inhibitor of biosynthesis of sterols from farnesyl pyrophosphate, a substrate for producing carotenoids which include astaxanthin, in an aqueous nutrient medium under aerobic conditions wherein the concentration of the inhibitor in the aqueous nutrient medium is within a range that gives less than a 50 % reduction of cell

growth as compared to cell growth in the absence of the inhibitor under carotenoids-producing conditions and cell growth is determined by measuring the optical density of a sample of the cultured medium at 660 nm..." Thus, An leads one skilled in the art away from the presently claimed process.

In addition, and as noted in the prior Response, An discloses that the "*P. rhodozyma* strains resistant to sterol biosynthesis inhibitors ... ***did not yield high producing strains***." (Page 118, right col., 8th to 6th line from the bottom) (emphasis added.) An further discloses that "***since the visual appearance or absorbance spectra of extracts did not resemble astaxanthin, we did not analyze the carotenoids produced in the presence of the inhibitors***." (Page 118, right col., 8th line from the bottom to Page 119, left col., line 2) (emphasis added.) For a scientific paper that explicitly set out to identify "...[m]utants with [i]ncreased [a]staxanthin [c]ontent" (Title), An apparently indicates that the visual appearance with regard to astaxanthin was such that analysis of the carotenoids for astaxanthin content was not even worth undertaking.

Furthermore, the Examiner did not take into consideration that An attempts to make no comparison as to whether or not the astaxanthin content of the isolated carotenoids is greater than that which results from cultivating in the absence of an inhibitor of biosynthesis of sterols from farnesyl pyrophosphate. Thus, the Examiner's assertion that "one of ordinary skill in the art would reasonably have expected some increase even though it might not be readily apparent to the naked eye" is unfounded and even if it were true (although it is contended that it is not), it would be of no moment because it fails to address the comparison recited in the claims.

One skilled in the art would understand the An disclosure, rather, as indicating that little or no astaxanthin was produced by the resistant strains, and that, in any event, the strains did not produce astaxanthin content greater than that which results from cultivating in the absence of such an inhibitor as claimed. Thus, An's results do not suggest or provide motivation for the claimed process in which astaxanthin content of carotenoids produced is "greater than that which results from cultivating in the absence of such an inhibitor".

Moreover, as noted above, An's use of resistant strains that were given an inhibitor concentration that gave greater than or equal to 90% kill teaches away from the claimed process of cultivating "in which the concentration of the inhibitor is within the range that gives less than a 50% reduction of cell growth as compared to cell growth in the absence of the inhibitor". An's results in terms of any astaxanthin produced, however the results may be characterized, fail to shore up the problematic aspects of the rejection.

Also contrary to An, the present application shows that good overproduction of astaxanthin can be obtained when using relatively low inhibitor concentrations as claimed. See Example 2 at Paragraphs 27-30. This is neither taught nor suggested by An. In view of An's approach, the results pertaining to the claimed process would have been unexpected.

For each of the foregoing reasons, the rejection has been rendered moot.

Reconsideration and withdrawal of the rejection are requested.

Accordingly, for the reasons set forth above, entry of the amendments, withdrawal of the rejections and allowance of the claims are respectfully requested. If the Examiner has any questions about this paper, please contact the undersigned.

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to Mail Stop RCE, Commissioner For Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on January 12, 2009.

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Respectfully submitted,

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